REMARKS

Receipt of the Office Action dated December 13, 2001 is acknowledged. Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 16, 18, 19 and 22 are pending in the application. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The amendments to the specification and the drawing are to correct clerical errors and do not constitute new matter. Throughout the application cDNA sequences were consistently and inadvertently referred to as "introns." Changing the mislabeled "intron" to "exon" does not constitute new matter as it is clear to one of ordinary skill in the art that the sequences referred to as "intron" sequences were, in fact, coding sequences as they were derived from mRNA. Thus, it is not new matter to simply correct the labeling of these sequences.

Support for the amendments to the claims can be found throughout the specification and the original claims. Specifically, support for claim 16 can be found throughout the specification and specifically at pages 19-22 which disclose at least sixteen splice variants of human telomerase. Support for the changes to claims 18, 19 and 22 can be found at page 8 of the specification which discloses the definition of variants regarding sequence identities.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Objection to the Specification

The PTO has objected to the usage of the terms exon and intron in the specification stating that the usage of these terms is confusing . OA at page 5. Applicants have amended the specification to (a) delete reference to exon or intron when such terms are not necessary to clarify the invention and (b) label all sequences which are found in telomerase cDNAs "exons." Therefore, withdrawal of this objection is respectfully requested.

No new matter is introduced by the amendments and such amendments are made to clarify the specification. The sequences presented in the specification are derived from cDNA sequences and therefore labeling such sequences as exons is appropriate.

The amendments to the specification and the drawing are to correct clerical errors and do not constitute new matter. Throughout the application cDNA sequences were consistently and mistakenly referred to as "introns." Changing the mislabeled "intron" to "exon" does not constitute new matter as it is clear to one of ordinary skill in the art that the sequences referred to as "intron" sequences were, in fact, coding sequences as they were derived from mRNA. Thus, it is not new matter to simply correct the labeling of these sequences.

The PTO stated that the words "an amplified" should be deleted at page 18, line 7 and that on page 56, line 2, Figure 1 should be Figure 2. OA at page 2. Accordingly, Applicants have made these corrections. Therefore, withdrawal of this objection is respectfully requested.

The PTO has objected to the specification because Figure 10A presents region 2 of human telomerase as only a partially known sequence while the sequence listing allegedly suggests that the sequence of region 2 (SEQ ID NO:30) is complete. OA at page 2. The PTO is correct in that only part of the sequence of region 2 is present in the text. However, partial sequence 2 is SEQ ID NO:29, not SEQ ID NO:30 and Applicants disagree that the sequence listing "suggests that the sequence of region 2 (SEQ ID NO:30) is complete." Specifically, the sequence listing is silent as to whether the sequence listed in SEQ ID NO:29 is a full length nucleotide sequence. Therefore, withdrawal of this objection is respectfully requested.

Objection to the Drawings

The PTO has stated that Figure 7 is illegible and confusing as to the usage of the terms exon and intron as well as pointing out that the position of fragment X is not shown. Regarding term usage, the attached red-lined Figure 7 has been amended to delete reference to "Exon(s) deleted" and has been amended to state "Intron(s) deleted." Pursuant to 37 C.F.R. § 1.121, a red-lined copy of the drawing is attached showing the changes. The amendment to Figure 7 introduces no new matter and is simply to correct the consistently erroneous use of "Exon" in the application. Approval of the changes to Figure 7 is respectfully requested.

Regarding the position of fragment X, the brief description of Figure 7 states that Panel A presents a "schematic representation of six splicing variants," thus, the position of fragment X is not part of the drawing. The position of fragment X is located at nucleotide 1764.

The PTO further states that Figure 10A presents two sequences labeled as "*". Under 37 C.F.R. § 1.121, applicants submit a red-lined copy of the drawing which shows the changes. The amendment to Figure 10A corrects a clerical error. The first "*" sequence is intron α and the second "*" is intron β. Support for these changes can be found in the sequence listing, SEQ ID NO:25 and SEQ ID NO:27. Approval of the changes to Figure 10 is respectfully requested.

Claims 19 and 22 Are Clear

The PTO has rejected claims 19 and 22 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because they recite the term "a portion of a vertebrate telomerase." While not acquiescing to the PTO's rejection, Applicants have amended claims 19 and 22 to recite a "fragment" of a human telomerase protein. Therefore, claims 19 and 22 satisfy the requirements of 35 U.S.C. § 112, second paragraph and the PTO is respectfully requested to withdraw the rejection.

Claims 19 and 22 Are Fully Described

The PTO has rejected claims 19 and 22 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. OA at page 6. Applicants respectfully traverse this rejection.

Claim 19 has been amended to state that the claimed protein is a fragment of the protein claimed in claim 18. Claim 18 is directed to a protein comprising specifically enumerated SEQ ID NO's. The PTO states that the genus of claimed polypeptides is a large variable genus, because there is an extremely large number of species of vertebrate and telomerase proteins that may be isolated from them. The PTO further argues that the specification fails to describe any other representative species by any identifying characteristics or properties other than being fragments of a vertebrate telomerase. OA at page 7. Applicants, however, strongly disagree as applicants have demonstrated possession of the subject matter of the claims. In *The Regents of the University of California v. Eli Lilly and Company*, 119 F.3d 1559 (Fed. Cir. 1997), the Federal Circuit stated that:

> [i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

One of skill in the art can distinguish the claimed sequences from any other claimed sequence and can identify many of the species that the claims encompass. Specifically, the genus in the claims are very well defined in that all of the species encompassed by the claimed genus originate from the disclosed splice variants of human telomerase protein. A person skilled in the art would be able to distinguish any nucleic acid species of the claimed genus by comparison with the sequence of human telomerase protein.

The court in *Eli Lilly* found that the claims at issue were not adequately described because the specification "did not specifically define any of the genes that fall within its definition. *It does not define any structural features commonly possessed by members of the genus that distinguish them from others*." *Eli Lilly* at 1562 (emphasis added). The present case is distinguished from *Eli Lilly* because a structural feature is defined which is commonly possessed by members of the genus. Specifically, all of the claimed fragments have the common structural feature that they are selected from a specifically identified sequence. Therefore, unlike in *Eli Lilly*, the present specification defines the genes which fall under the claimed genus.

The PTO has also rejected claim 18 under 35 U.S.C. § 112, second paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. OA at page 7. Applicants respectfully traverse this rejection.

The PTO specifically states that

> [i]n the view of the lack of any structural and functional characteristics of the variants encompassed b the scope of the claim, Applicants failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention.

OA at page 7.

Applicants respectfully disagree. While not acquiescing to the PTO's rejection, Applicants have amended claim 18 to further define "variant." A variant is an amino acid sequence which has at least 75% amino acid identity with the amino acid sequences presented in Figure 11. One of skill in the art would readily be able to distinguish the species of the genus of variants because all of the variants claimed have the specific homology to the claimed amino acid sequences. As such, the rejection under 35 U.S.C. § 112, first paragraph for allegedly failing to satisfy the written description requirement is improper and should be withdrawn.

Claims 16, 19 and 22 Are Fully Enabled Over Their Entire Scope

The PTO has rejected claims 16, 19 and 22 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the variant of human telomerase described by SEQ ID NO:46 and its fragments that may be encoded by the introns, does not reasonably provide enablement for any vertebrate telomerase, its fragments or fragments that are 10-100 amino acids in length. OA at page 8. Applicants traverse this rejection.

The PTO states that the claims are broader than the enablement provided by the disclosure with regard to the extremely large number of all known and unknown enzymes having said the activity and originating from all vertebrates, and fragments of any vertebrate telomerase or fragments thereof. Claims 16, 19 and 22 have been amended such that the claims are directed to nucleic acid molecules comprising splice variants of human telomerase protein. The sequence of human telomerase protein is given in the specification, along with a number of its splice variants. In view of these amendments to the claims, Applicants believe that the Examiner's enablement rejection has been overcome. Applicants therefore respectfully request withdrawal of this rejection.

Claim 18 has been rejected by the PTO because allegedly "the specification, while not being enabling for the variant of human telomerase described by SEQ ID NO:46, does not reasonably provide enablement for any variants of SEQ ID NO:6 (sic) . . ." OA at page 10. Applicants respectfully traverse this rejection.

The PTO states that the nature and breadth of the claimed invention encompasses any variant of the protein encoded by SEQ ID NO:46. Applicants have amended claim 18 to recite that the variant must have at least 75% amino acid identity with the amino acid sequences presented in claim 11.

The PTO states that methods of gene mutation and expressing mutated proteins are well known in the relevant art, and the skills of the artisans are highly developed. OA at page 9. The PTO then states that no one skilled in the art is able to perform all possible modifications of SEQ ID NO:46. OA at page 10. Applicants respectfully state that a determination that a claim is enabled does not rest on whether the claim encompasses a large number of species. If the skilled artisan can practice the claim over its full range, without *undue experimentation*, the claims are enabled. *In re Fisher*, 166 USPQ 19 (CCPA 1970). The test of enablement is not whether any experimentation is

necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).

As the PTO stated above, the methods of gene mutation and expressing mutated proteins are well known in the relevant art, and the skills of those practicing this technology are highly developed. Any experimentation that may be necessary to practice the full range of the invention would therefore not be undue. Withdrawal of this rejection is therefore respectfully requested.

Claims 16, 18, 19 and 22 Are Patentable Over the Prior Art of Record

The PTO has rejected claims 16, 18, 19 and 22 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,093,809 to Cech *et al.* ("the '809 patent"). Applicants traverse this rejection.

In particular, the Office Action states the '809 patent discloses the human telomerase protein (SEQ ID No:225) and alleges that this sequence is identical to the sequence of human telomerase gene of the instant application (SEQ ID NO:2).

While not acquiescing to the PTO position, Applicants have amended the claims to recite an isolated nucleic acid molecule comprising a splice variant of human telomerase protein. The '809 patent does not disclose or suggest the splice variants claimed in the instant application.

The PTO states that SEQ ID NO:46 of the instant application, which is the human telomerase lacking the α intron, is comprised by the protein disclosed in the '809 patent. Applicants respectfully disagree. The splice variants of the instant application are not encompassed by SEQ ID NO:225 of the '809 patent. The polypeptide disclosed in SEQ ID NO:225 encompasses additional amino acids in the middle of the polypeptide as compared to SEQ ID NO:46. Claims comprising a protein which comprises the contiguous amino acid sequence of SEQ ID NO:46 does not encompass SEQ ID NO:225 of the '809 patent. Therefore, withdrawal of this rejection is therefore respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date: May 13, 2002

By ______________ 40,413

for Richard C. Peet
Attorney for Applicant
Registration No. 35,792

FOLEY & LARDNER
Customer Number: 22428
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5483
Facsimile: (202) 672-5399

Version with markings to show changes made

In the claims:

16. (Amended) An isolated protein comprising a [vertebrate telomerase protein] splice variant of human telomerase protein.

18. (Twice Amended) The protein of claim 16, wherein the protein comprises one of the amino acid sequences presented in [Figure 1 (SEQ ID NO:2) or] Figure 11 (SEQ ID Nos. 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82, 84-86), or variant thereof, wherein said variant has at least 75% amino acid identity with said amino acid sequences presented in Figure 11.

19. (Amended) A [portion of a vertebrate] fragment of said splice variant of human telomerase protein according to claim 16.

22. (Amended) The [portion] fragment of claim 19, wherein [the portion] said fragment is from 10 to 100 amino acids long.

In the specification:

Page 6, starting at line 19 and ending at line 30:

Figure 5 shows the results of amplification of cDNAs synthesized from various tissues. Amplification is performed using primers from the hT1 cDNA sequence [that span an intron in the hT1 gene,] and the products are blotted and probed with a radiolabeled oligonucleotide from the hT1 sequence. Amplification is also performed on the same samples with a pair of primers from the β-actin gene as a loading control. a: hT1 cDNA control; b: human genomic DNA control; c: no template control; d: normal colon RNA; e: normal testis RNA; f: normal lymphocyte RNA; g: melanoma RNA (cerebral metastasis); h: melanoma RNA (subcutaneous ankle metastasis); i: melanoma RNA (liver metastasis); j: melanoma RNA (lung metastasis); k: melanoma RNA ([axillary] auxiliary lymph node metastasis); l: melanoma RNA (skin metastasis); m: breast carcinoma RNA; n: breast carcinoma RNA; o: breast carcinoma RNA; p: breast carcinoma RNA.

Page 17, starting at line 3 and ending at line 22:

Methods for obtaining fragments are well-known in the art. Portions that are particularly useful within the context of this invention contain the catalytic site, individual RTase motifs, the putative [intronic] exonic sequences (see Figure 10), and the like. Oligonucleotides are generally synthesized by automated fashion; methods and apparatus for synthesis are readily available (*e.g.*,

Applied Biosystems Inc, CA). Oligonucleotides may contain non-naturally occurring nucleotides, such as nucleotide analogues, a modified backbone (*e.g.*, peptide backbone), nucleotide derivatives (*e.g.*, biotinylated nucleotide), and the like. As used herein, oligonucleotides refers to a nucleic acid sequence of at least about 7 nucleotides and generally not longer than about 100 nucleotides. Usually, oligonucleotides are between about 10 and about 50 bases, more often between about 18 and about 35 nucleotides long. Oligonucleotides can be single-stranded or in some cases double-stranded. As used herein, portions of a nucleic acid refer to a polynucleotide that contains less than the entire parental nucleic acid sequence. For example, a portion of telomerase coding sequence contains less than a full-length telomerase sequence. A 'portion' is generally at least about seven nucleotides, and may be as many as 10, 20, 25 or more [nnucleotides] <u>nucleotides</u> in length. A fragment refers to a polynucleotide molecule of any length and can encompass an oligonucleotide, although more usually, but not to be limiting, the term oligonucleotide is used to denote short polynucleotides and the term fragment is used to denote longer polynucleotides.

Page 17, paragraph starting at line 23 and ending at page 18, line 7:

Oligonucleotides for use as primers for amplification and probes for hybridization screening may be designed based on the DNA sequence of human telomerase presented herein. Oligonucleotide primers for amplification of a full-length cDNA are preferably derived from sequences at the 5' and 3' ends. Primers for amplification of specific regions are chosen to generate products of an easily detectable size. In preferred embodiments, primers are chosen that flank the sequences subject to alternative RNA splicing. In preferred embodiments, one set of primers is chosen such that both the product that spans spliced-in sequence as well as the product that spans spliced-out sequence are suitable sizes to be detected under the same reaction conditions. In other embodiments, two sets of primers are used to detect the alternative spliced RNAs. For example, one set of primers flanks the splice junction in order to detect a spliced-out product. The second set of primers may be derived very close to the junction (such that a spliced-out amplification product is the same size or barely larger than a primer-dimer length) or one or more of the set may be derived from the spliced-in sequence (such that the spliced-out RNA would not yield any product). [An amplified]

Page 19, starting at line 13 and ending at line 22:

In addition to the reference telomerase DNA and protein sequences presented in Figures 1, several RNA splice variants are observed. Although some of the variants may reflect incompletely processed mRNA, it is noteworthy that such variants are abundant in an RNA sample (LIM1215) preselected for polyadenylated mRNA. These findings, together with their clustering in the RT domain, suggest that the insertion variants more likely reflect regulation of hT1 protein expression. For example, variants [in which exons are deleted] (see α, β, Fig. 7) are likely alternative mature coding for variant proteins. Additional evidence in support of alternative proteins comes from sequence analysis of cDNA clones identified in a LIM1215 cDNA library that contained both deletions and insertions compared to the reference sequence.

Page 19, starting at line 23 and ending at line 29:

At least seven different putative [introns] exons appear to be retained in mRNAs (see Figure 7, which displays 6 of the 7 [introns] exons). The [introns] exons may be independently retained, thus, a particular mRNA may have none, any one, two, etc. up to seven [introns] exons. The maximum number of different mRNAs resulting from seven independently spliced [introns] exons is 2^7, or 128 different mRNAs. DNA sequences of these [introns] exons are presented in Figure 10. The 5' most [intron] exon, called sequence "X", is an unknown length, and only a partial sequence is presented.

Page 20, starting at line 1 and ending at line 7:

The reference telomerase sequence (Figure 1) includes [intron] exon α and [intron] exon β. In the following discussion, the effect of presence/absence and location of each [intron] exon is presented on the basis that it is the only alteration. It will be appreciated that a particular [intron] exon may alter the sequence of the translated product, regardless of whether other [introns] exons are spliced in or out. For example, the presence of [intron] exon 1 results in a frameshift and truncated protein, regardless of whether [introns] exons α, β, 2 or 3 are spliced in or out.

Page 20, starting at line 8 and ending at line 13:

The presence of [intron] exon "X" results in a truncated protein that contains approximately 600 N-terminal amino acids and lacks all of the RTase motifs. The presence of [intron] exon "Y" at base 222 results in a frameshifted protein that terminates within three codons past the [intron] exon. As the Y [intron] exon is very GC rich, approximately 78%, which is difficult to sequence, it is possible that [intron] exon Y causes an insertion of about 35 amino acids and not a frameshift.

Page 20, starting at line 14 and ending at line 16:

[Intron] Exon 1 at nucleotide 1950 is 38 bp and its presence in mRNA causes a frame-shift and ultimate translation of a truncated protein (stop codon at nt 1973). This truncated protein contains only RTase domains 1 and 2.

Page 20, starting at line 17 and ending at line 22:

[Intron] Exon α, located from bases 2131-2166 is frequently observed spliced out of telomerase mRNA. A protein translated from such an RNA is deleted for 12 amino acids, removing RTase motif A. This motif appears to be critical for RT function; a single amino acid mutation within this domain in the yeast EST2 protein results in a protein that functions as a dominant negative and results in cellular senescence and telomere shortening.

Page 21, starting at line 4 and ending at line 13:

[Intron] Exon 2 at base 2843 contains an in-frame termination codon, resulting in a truncated protein that has the entire RTase domain region, but lacks the C-terminus. As the C-terminus may play a regulatory role, protein activity will likely be affected. When [intron] exon 3 is retained, a smaller protein is also produced because the [intron] exon contains an in-frame stop codon. Thus, the protein has an altered C-terminal sequence. What activity such proteins might have is currently unknown. The crystal structure of the HIV-1 reverse transcriptase demonstrates that a short form of the protein (p51) that lacks the RNAase domain is inhibited by the C-terminal 'connection' folding into the catalytic cleft. If hT1 is assumed to adopt a similar structure to HIV-RT, then C-terminal hT1 protein variants may reflect a similar mechanism of regulation.

Page 21, starting at line 14 and ending at line 24:

In addition to variants that lack the reference C-terminal domain, a variant with [intron] exon 3 at base 2157 expresses an alternative C-terminal domain. Furthermore, the coding region donated by [intron] exon 3 has a potential SH3 binding site, SGQPEMEPPRRPSGCVG, which matches the consensus c-Abl SH3 binding peptide (PXXXXPXXP) found in proteins such as ataxia telangiectasia mutated (ATM). A second example of this motif is found within the N-terminal end of the hT1 protein in the peptide HAGPPSTSRPPRPWDTP. Other alternative C-terminal domains are found in telomerase cDNAs; the EST12462 (GenBank Accession No. AA299878) has about 50 bases of identical sequence up to base 2157 and then diverges from the reference telomerase sequence as well as [intron] exon 3. This new sequence has an internal stop codon in 50 bases that would result in a truncated C-terminus.

Page 22, starting at line 1 and ending at line 8:

The following table summarizes the splice variants and resulting proteins. For simplicity, only a single variant is listed for each resulting protein. Furthermore, as noted above, the presence of the Y [intron] exon appears to cause a frameshift resulting in a truncated protein, but may cause an insertion. Thus, each reading frame of the Y [intron] exon is presented and the table is constructed as if the insertion does not cause a truncated protein. An independent assortment of these known [introns] exons would lead to 128 different mRNA sequences. The DNA and amino acid sequences for the variants in Table 1 are presented in Figure 11.

Page 26, starting at line 20 and ending at line 29:

Peptides of particular interest within the context of this invention have the sequence of the [intron] exon sequences (Figure 10), the RTase motifs, and the like. In certain embodiments, telomerase proteins have the amino acid sequences presented in Figures 1 or 11, or a portion thereof which is at least 8 amino acids in length (and may be 10, 15, 20 or more amino acids in length). In other embodiments, the protein has one or more amino acid substitutions, additions, deletions. In yet other embodiments, the protein has an amino acid sequence determined by a nucleic acid sequence that hybridizes under normal stringency conditions to the complement of any of the sequences in Figure 11. As indicated above, variants of telomerase include allelic variants.

Page 30, starting at line 1 and ending at line 15:

As discussed above, in preferred embodiments, expression of the various RNA species is monitored. The different species may be assayed by any method which distinguishes one of the species over the others. Thus, length determination by Northern, RNase probe protection, cloning and amplification are some of the available methods. In preferred embodiments, RNase probe protection and amplification are used. For RNase probe protection, the probe will generally be a fragment derived from the junction of the reference sequence and the [intron] exon sequence or derived from the sequence surrounding the [intron] exon insertion site. For example, a fragment of the reference telomerase that spans nucleotide 1950-1951 (*e.g.*, nucleotides 1910-1980) will protect the reference sequence as a 71 base fragment, but will protect a telomerase with [intron] exon as two fragments of 41 and 30 bases. In contrast, a fragment that contains nucleotides 1910-1950 and 30 bases of [intron] exon 1 will protect an [intron] exon 1 variant as a 71 base fragment and the reference telomerase as a 41 base fragment. Fragments for RNase probe protection are chosen usually in the range of 30 to 400 bases and are positioned to yield readily distinguishable protection products.

Page 37, starting at line 1 and ending at line 17:

Another inhibitor of the present invention is antisense RNA or DNA to telomerase coding or non-coding sequence. Antisense nucleic acids directed to a particular mRNA molecule have been shown to inhibit protein expression of the encoded protein Based upon the telomerase sequences presented herein, an antisense sequence is designed and preferably inserted into a vector suitable for transfection into host cells and expression of the antisense. The antisense may bind to any part of the hTI RNA. In certain embodiments, the antisense is designed to bind specifically to one or more variants. Specific binding means that under physiological conditions, the antisense binds to RNAs that have the complementary sequence, but not other RNAs. Because telomerase RNAs that contain any particular [intron] exon sequence may be a heterogeneous group of variants due to independent assortment of splice variants, more than one species of RNA may be bound and inactivated. The antisense polynucleotides herein are at least 7 nucleotides long and generally not longer than 100 to 200 bases, and are more typically at least 10 to 50 bases long. Considerations for design of antisense molecules and means for introduction into cells are found in U.S. Patent Nos. 5,681,747; 5,734,033; 5,767,102; 5,756,476; 5,749,847; 5,747,470; 5,744,362; 5,716,846).

Page 39, starting at line 26 and ending at page 40, line 6:

Therefore, the [intron] exon sequences may be especially useful for diagnostic applications. For example, detection and identification of diseases, such as cancer, aging, wound healing, neuronal regeneration, regenerative cells (*e.g.*, stem cells), may be important preludes to determining effective therapy. In this regard, detection of wound healing can facilitate development and identification of an ameliorative compound. Currently, wound healing assays are expensive and time consuming, whereas an amplification or hybridization-based assay would be quick and cost effective. In any of these applications, detection may be quantitative or qualitative. In a qualitative assay, a particular amplification primer pair or hybridization probe for one of the variant sequences (*e.g.*, [introns] exons that are variably spliced) can be used to detect the presence or absence of the variant sequence.

Page 40, starting at line 29 and ending at page 41, line 4:

For amplification assays, primer pairs that either flank the [introns] exons or require the presence of the [intron] exon for amplification are desirable. Many such primer pairs are disclosed herein. Others may be designed from the sequences presented herein. Generally, the primer pairs are designed to only allow amplification of a single [intron] exon, however, in some circumstances detection of multiple [introns] exons in the same RNA preparation may be preferred.

Page 55, starting with line 21 and ending at page 56, line 3:

To test the hypothesis that such a transcript exists, a primer, HTM2028F, is designed such that amplification ensues only when the 36 bp fragment was missing. Amplification using HTM2028F and HT2026F primers in combination with HT2356R demonstrate that transcripts containing the 182 bp fragment but missing the 36 bp fragment are present in LIM1215 RNA (Figure 9, lanes a and b). The same top strand primers (HTM2028F and HT2026F) in combination with HT2482R primer amplify a number of products from LIM1215 RNA (Figure 9, lanes c and d), most of which represent bands 1- 4 as determined by direct sequence analysis of PCR products. An amplified fragment of 650 bp using HTM2028F and HT2482R primers represents another, not yet fully characterized, alternatively spliced telomerase variant in the RT-MotifA/RT Motif B region. For clarity of presentation, the protein sequence giving the best match with *Euplotes* and *S. cerevisiae* proteins is presented in [Figure 1] Figure 2 as the reference sequence.

Page 56, starting at line 4 and ending at line 24:

Specifically, there are at least seven inserts or [introns] exons that can be present (or absent) from telomerase RNA. (1) The 5'-most sequence (Y) is located between bases 222 and 223. (2) the insert (X) is located between bases 1766 and 1767. A partial sequence is determined and is presented in Figure 10. Termination codons are present in all three reading frames. Thus, a truncated protein without any of the Rtase motifs would be produced. (2) A sequence, indicated as "1" in Figure 7, is located between bases 1950 and 1951. This [intronic] exonic sequence is 38 bp (Figure 10) and appears to be present in ALT and most tumor lines. The presence of this sequence adds 13 amino acids and shifts the reading frame, such that a termination codon (TGA) is in frame at nucleotide 1973. (3) A sequence, indicated as "α" in Figure 7, is located between bases 2130 and 2167. This sequence is 36 bp (Figure 10) and its absence removes RTase motif "A" but does not alter the reading frame. (4) A sequence, indicated as "β" in Figure 7 is present between bases 2286 and 2469. The insert is 182 bases (Figure 10) and its absence causes a reading frame-shift and a termination codon in RTase motif 5 at nucleotide 2604. (5) The sequence "2" in Figure 7 is present between bases 2823 and 2824. Its length is undetermined; its partial sequence is presented in Figure 10. The presence of this insert causes a truncated telomerase protein, as the first codon of the insert is a termination codon. (6) The sequence "3" is a 159 bp insert (Figure 10) between bases 3157 and 3158. Its presence leads to a telomerase protein with an altered COOH-terminus. The insert contains a stop codon. Moreover, sequence "3" has a putative binding site for the SH3 domain of c-*abl* (PXXXXPXXP; PEMEPPRRP).